REMARKS

Claims 26-32 are pending in the present application.

Claim 26 has been amended herein to identify a further novel and non-obvious aspect of the invention which is that the re-folding buffer and folding process claimed by the Applicant do not require a chaotropic agent. This is a material aspect of the Applicant's claimed invention which, in part, differentiates it from prior art disclosures.

Rejections under 35 U.S.C. § 102(e):

The Examiner has rejected claims 26 – 32 under 35 U.S.C. § 102(e) in view of the reference Builder, et al. US Patent # 5407810. The Examiner mentions that the 35 U.S.C. § 102(e) rejection encompasses Rudolph, R. (reference u13). However, the Applicant notes that the Rudolph reference is not a 35 U.S.C. § 102(e) reference since it is not a patent or patent application, but a journal article, and thus cannot be an anticipating reference under 35 U.S.C. § 102(e).

The Applicants address the Examiner's rejection of claims 26 – 32 under 35 U.S.C. § 102(e) in view of Builder, et al. The invention of Builder, et al. requires the additional element of chaotropic agents to re-fold the proteins disclosed by Builder in the processes disclosed by Builder. The Applicant's invention is novel in part because it is a simple one step procedure which does not require chaotropic agents as a required element to provide re-folded biologically active proteins.

The Examiner has stated that a reference patent under 35 U.S.C. § 102(e) is available for all that it fairly discloses to one of ordinary skill in the art. Builder disclose that a chaotropic agent must be used for re-folding proteins in the processes disclosed therein. The Examiner has stated that the methods or processes disclosed by Builder et al. do not rely solely on the presence of a chaotropic agent. It is true that builder's disclosed processes which include, isolating, solubilizing, extracting and refolding proteins to an active configuration, does not rely solely on a chaotropic agent. However, Builder's invention does require the use of chaotropic agents to provide re-folded proteins and the required element of a chaotropic agent is identified in each re-folding step disclosed or claimed therein.

In Builder, et al., the Summary of the Invention, each example, and each claim, explicitly identify the requirement of a chaotropic agent for q process of re-folding proteins. Each aspect of the

invention in columns 5 and 6 of Builder identifies that a chaotropic agent is present in the re-folding process disclosed therein. Builder, in column 19 lines 32-45, identify that a key element or ingredient of the refoldinf buffer of Builder is a chaotrope. Example I of Builder identifies a refolding "step G" for IGF-1 derived from E. Coli expression which uses the chaotrope urea (please see Col. 26, lines 17-21). Example II discloses the use of the same refolding step G which contains urea as in Example I.

Examples III and IV of Builder disclose the use of PEG for isolation of the IGF peptide from cell lysates. However, this element is not claimed in the refolding process nor is it an element required for refolding. The disclosure of PEG as an element of the disclosed processes in Builder pertains to a method of isolating a peptide and separating solids in various phases of solutions of various content of PEG prior to re-folding. Builder indicates that the PEG fractionation is used to identify optimum regions of PEG phases for separation of IGF and cell solids (please see Col. 27, lines 37-60). Thus the purpose of using PEG solution for isolation of peptides is not to refold the protein (please also see Col. 4, line 56 to column 5, line 21).

Example V of Builder et al. discloses the use of the refold buffer of step G which contains a chaotropic agent as disclosed in Example I to refold IGF.

Example VI of Builder et al. discloses a comparison example to illustrate the effect of pH on phase separation in PEG two phase solutions. No refolding of proteins was carried out or disclosed in Example VI of Builder et al.

Example VII of Builder et al. discloses the use of the refold buffer of Step G of Example I to refold IGF.

Example VIII of Builder et al. discloses the use of the refold buffer of Step G of Example I to refold IGF.

Example IX of Builder et al. discloses the use of a "reduced IGF-1 stock solution" which contains the chaotrope urea at 2 molar concentration.

Example X discloses the use of the refolding solution identified in Example IX.

Claim 1 (column 38, line 62, column 39, line 2) claims a method of refolding, to an active configuration, a polypeptide of interest under conditions which include a chaotropic agent. Claims 2-24 are dependent thereon.

Claim 25 claims a method which requires the use of a chaotropic agent for re-folding a protein.

Claim 26 claims a method which requires the use of a chaotropic agent for re-folding a protein. Chaims 27-29 are dependent thereon.

Whether the chaotropic agent is added before or at initiation of re-folding of the proteins, the processes disclosed in Builder always requires chaotropic agents to re-fold proteins.

Thus, even if the processes disclosed in Builder et al do not rely solely on chaotrope the y do indeed require the element of a chaotropic agent to re-fold proteins. Applicant's invention does not require the element of a chaotrope. Therefore, Builder et al. do not anticipate the Applicant's claimed invention. The fact that Applicant's invention achieves re-folding of proteins with less or different elements than those required by Builder et al. provide the requisite novelty to overcome the pending rejection. The Applicant respectfully requests that the Examiner withdraw the rejection of claims 26 – 32 based on 35 U.S.C. § 102(e) based on the foregoing.

The Examiner has rejected claims 26 – 32 under 35 U.S.C. § 102(e) or in the alternative under 35 U.S.C. § 103(a) over Builder in view of Rudolph. It is not clear on what basis this rejection is made since there exists a provisional rejection under 35 U.S.C. § 102(e)/35 U.S.C. § 103(**c**) for claims which may be anticipated or obvious over prior art for which there is ownership by a common assignee. This is not the case for the present invention since there is no common inventorship. If the rejection is one of 35 U.S.C. § 102(e) then this rejection pertains to the Builder et al reference only and that rejection is addressed above in this paper. Rudolph cannot be an anticipating reference under 35 U.S.C. § 102(e) since it is not a patent or patent application. The other possibility is that the rejection is intended to be one of 35 U.S.C. § 103(a) over Builder in view of Rudolph and the Applicant addresses that type of rejection below.

Rejections under 35 U.S.C. § 103:

As stated in Applicants previous response and also herein-above there is no suggestion that the method disclosed by Builder et al. for re-folding of proteins can proceed without using a chaotropic agent. The Examiner states that Builder teach the use of producing biologically active TGF–beta 2 and TGF-beta 3 using a folding buffer comprising glutathione and DMSO or DMF. The Examiner also states that the Applicant uses the language "consisting essentially of" to claim elements of the folding buffer of the present invention. The Examiner states that since the Applicant has not produced evidence that the additional elements required in the method disclosed in Builder et al. affect the basic and novel characteristics of the present invention that the language "consisting essentially of" includes the additional elements of Builder et al. The

Applicant has amended claim 26 to more succinctly identify the fact that no chaotropic agent is used in the present invention and thus the additional elements required by Builder would affect the basic and novel characteristics of the claimed invention.

The Applicant further asserts that since Builder et al. teach away from the Applicant's invention, in that Builder require the use of a chaotropic agent and the Applicant's claimed invention does not require chaotropic agents, that Builder et al. would not suggest or motivate one skilled in the art to employ the simple and elegant folding buffer of the Applicant's invention.

Rudolph teaches general ways to bring about re-folding of proteins and identifies several methods which have been used to re-fold for specific. Rudolph does not show how to re-fold TGF-beta. Rudolph does not teach the sue of a re-folding buffer which utilizes an organic solvent as a buffer medium for re-folding as disclosed by the Applicant. At best, with respect to the Applicant's invention, Rudolph teaches that re-folding of proteins is a highly variable process and that the appropriate folding buffer must be selected based on the particular nature of each protein which is sough to be re-folded.

Based on the amendment to the claim 26 and the foregoing remarks, the Applicants assert that that one skilled in the art would not be motivated to combine the teachings of Builder and Rudolph to produce the Applicants present claimed invention. The Applicants thus respectfully request that the Examiner withdraw the rejections under 35 U.S.C. § 103(a) based thereon.

The Applicants believe that the application is now in condition for allowance and respectfully request early notice to that effect. If it will advance prosecution of the Application the Examiner is urged to contact the Applicants' undersigned counsel at the telephone number listed below.

Respectfully submitted,

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